REMARKS

Claims 1, 33 and 41 have been amended. Claims 6, 38 and 45 have been cancelled without prejudice to their subsequent reintroduction into this application or their introduction into a related application. Upon entry of this paper, claims 1-4, 8, 9, 32-35, 39-43 and 47-49 will be pending and under consideration in this application.

Claims 1, 33, and 41 have been amended to recite that the anti-angiogenesis factor is "selected from the group consisting of angiostatin and an antibody that binds preferentially to vascular endothelial growth factor" and the photosensitizer is "selected from the group consisting of lutetium texaphyrin and benzoporphyrin derivative." Support for the amendments may be found throughout the application as filed including, for example, the paragraph bridging pages 9 and 10, and page 12, lines 2-7 and 16-19. Applicants believe that the amendments introduce no new matter.

The rejections and objection are addressed below in the order in which they appear in the outstanding Office Action.

Rejection Under 35 U.S.C. §112, First Paragraph - Enablement

According to section 4 of the outstanding Office Action, claims 1-4, 6, 8-9, 32-35, 38-43, 45 and 47-49 presently stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Applicants submit that claims 6, 38 and 45 have been cancelled thereby rendering this rejection moot as it relates to these claims. Applicants respectfully traverse this rejection to the extent that it is maintained over the remaining claims, as amended, and request that the rejection be reconsidered and withdrawn.

The Office Action indicates that given the "indefinite number of undisclosed 'tetrapyrrole derivative' and the lack of guidance as to the binding specificity of the antibody in the claimed method, it is unpredictable which undisclosed 'tetrapyrrole derivative' in combination with either angiostatin or anti-VEGF antibody would be useful as a method for treating unwanted choroidal neovasculature associated with age-related macular degeneration, let alone any idiopathic disorders, and any inflammatory diseases." Although Applicants disagree, in order to promote

prosecution, Applicants have amended independent claims 1, 33 and 41 and the claims depending therefrom, to recite that (i) the photosensitizer useful in the practice of the claimed invention is selected from the group consisting of a lutetium texaphyrin photosensitizer and a benzoporphyrin derivative photosensitizer, and (ii) the anti-angiogenesis factor is selected from the group consisting of angiostatin and an antibody that binds preferentially to vascular endothelial growth factor. Applicants submit that the meaning of the term "binds preferentially" is discussed on page 12, lines 16-19 of the application as filed.

The test for enablement is whether persons skilled in the art can make and use the invention without undue experimentation (see, MPEP 2164.01; see also, MPEP 2164.02). Applicants submit that the claims, as amended, are not unduly broad and that a skilled artisan in possession of Applicants' disclosure would be fully enabled to practice the claimed methods of treating unwanted choroidal neovasculature (CNV) without undue experimentation.

As discussed in Applicants previous Amendment and Response, the courts have identified several factors for assessing whether a disclosure requires undue experimentation. These factors include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance provided, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the art, and (8) the breadth of the claims. *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). Applicants respectfully submit that, under the *Wands* test, the specification enables one of ordinary skill in the art to practice the claimed invention without undue experimentation. Each of the *Wands* factors are discussed in more detail below.

Nature of the Invention and Breadth of the Claims

The present invention is directed to a photodynamic therapy (PDT)-based method of treating unwanted CNV comprising endothelial cells in a mammal. Independent claims 1, 33 and 41 all require the steps of: (a) administering to the mammal an anti-angiogenesis factor selected from the group consisting of angiostatin and an antibody that binds preferentially to vascular endothelial growth factor in an amount sufficient to permit an effective amount to localize in the CNV; (b) administering to the mammal an amount of a tetrapyrrole derivative photosensitizer

sufficient to permit an effective amount to localize in the CNV selected from the group consisting of lutetium texaphyrin and benzoporphyrin derivative; and (c) irradiating the CNV with laser light to activate the photosensitizer, wherein the activated photosensitizer induces damage to the CNV resulting in its occlusion.

State of the Prior Art, and Relative Skill of Those in the Art

Applicants submit that, at the time the invention was made, the state of the art was advanced and the level of skill in the art was high.

The art cited in the specification, cited on the PTO-1449 forms of record, or applied by the Examiner, all show the advanced state of the art. For example, U.S. Patent No. 5,707,986 (already of record) shows that, prior to the filing of the instant application, it had been possible to selectively occlude CNV in primate eyes using green porphyrin-based PDT. Furthermore, the disclosures in the art of record evidence the fact that, as found in *Wands*, "[t]here was a high level of skill in the art at the time the application was filed." 8 USPQ2d at 1406.

Amount of Direction or Guidance Provided, and the Quantity of Experimentation

Applicants have provided extensive guidance regarding the practice of the invention. The specification provides a detailed discussion with respect to the choice of an appropriate angiogenesis factor, its dosage and its mode of administration, the choice of an appropriate photosensitizer, its dosage and its mode of administration, and the irradiation conditions (for example, the time between dye administration and light activation, the fluence, the irradiance, and the wavelength of the laser light) to activate the photosensitizer.

For example, with respect to the photosensitizer, page 9, lines 12-29 of the specification discuss exemplary tetrapyrrole derivative photosensitizers useful in the practice of the invention (including the lutetium texaphyrin photosensitizer and a benzoporphyrin derivative photosensitizer), and direct the artisan to particular citations for further information concerning those photosensitizers. Furthermore, the specification provides a detailed discussion of suitable formulations for the photosensitizer (see page 10, lines 16 through page 11, line 11 of the application as filed), dosages of the photosensitizer (see page 13, lines 13-18 of the application as

filed), and modes of administration of the photosensitizer (see page 13, lines 1-6 of the application as filed).

In addition, with regard to the irradiation parameters, the specification provides a detailed discussion of the optimal wavelength values for the laser light (see, for example, page 13, lines 19-27 of the application as filed), the choice of appropriate irradiance values (see, for example, page 14, lines 8-13 of the application as filed), the choice of appropriate fluence values (see, for example, page 14, lines 5-8 of the application as filed) and the timing of irradiation after administration of the photosensitizer (see, for example, page 14, lines 14-30 of the application as filed). In addition, the specification discusses methods for monitoring the efficacy of photodynamic therapy (see, for example, page 15, lines 1-7 of the application as filed).

With regard to an anti-angiogenesis factor useful in the practice of the invention, the claims as amended now require angiostatin and/or an antibody that binds preferentially to anti-vascular endothelial growth factor. These anti-angiogenesis factors are described on page 16 of the application as filed. The specification provides a detailed description of the dosages (see, for example, page 18, line 26 through page 19, line 4 of the application as filed) and modes of administration (see, for example, page 19, lines 5-16 of the application as filed) of these anti-angiogenesis factors.

<u>Working Examples</u>

Applicants respectfully submit that the courts have long held that "there is no magical relationship between the number of representative examples and the breadth of the claims; the number and variety of examples are irrelevant if the disclosure is 'enabling' and sets forth the 'best mode contemplated.'" *In re Borkowski*, 422 F.2d 904, 910, 164 USPQ 642 (CCPA 1970).

Notwithstanding the foregoing, Applicants submit that the specification provides specific working examples. By way of example, Example 1, appearing on pages 23-26 of the specification describes a PDT protocol using the tetrapyrrole derivative photosensitizer, Lu-Tex, in combination with the anti-angiogenesis factor, angiostatin. The Example describes the type of protocol that may be used *in vivo*.

The Office Action on page 6, however, states that, "the specification does not teach how to extrapolate data obtained from *in vitro* proliferation and apoptosis assays to the development of effective *in vivo* human therapeutic compositions as a method of treating unwanted choroidal neovasculature." Applicants submit that the specification provides adequate guidance to those skilled in the art on how to provide an effective treatment *in vivo*.

Furthermore, in the previous Amendment and Response, Applicants referred the Examiner to a copy of an abstract (made of record as citation C115) which was presented in May of 2003 at the Annual Meeting of the Association of Research in Vision and Ophthalmology in Fort Lauderdale, Florida. The abstract discusses a series of experiments performed in accordance with the teachings of the specification that demonstrate that a PDT protocol for the treatment of CNV *in vivo* may be more effective if the recipient is pre-treated with an anti-angiogenesis factor. The results demonstrate that, at the dosages of angiostatin used in these experiments, angiostatin alone did not prevent the development of CNV. However, continuous administration of angiostatin prior to PDT using the tetrapyrrole derivative Verteporfin significantly reduced the development of CNV relative to PDT alone.

In addition, in the previous Amendment and Response, Applicants referred the Office to citation C101, which is a summary of the Jules Gonin Lecture given by Dr. Joan W. Miller (a co-inventor of the claimed subject matter) to the Macula Society in September 2002 at the time she received the Club Jules Gonin Retina Research Award from the Club Jules Gonin. The third and fourth pages, for example, of the article summarize *in vivo* experiments combining PDT using Verteporfin with the anti-angiogenesis factor, anti-vascular endothelial growth factor antibody (RhuFab V2). The third full paragraph on page four states that, "preclinical results show that RhuFab V2 intravitreal injection plus Verteporfin PDT is safe and appears to result in a greater reduction in angiographic leakage from CNV than PDT alone."

Predictability of the Art

Notwithstanding the assertion in the Office Action that the "pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity," Applicants submit that the specification provides adequate guidance to those skilled in the art

commensurate with the scope of the claimed invention. Moreover, as described above, the specification itself provides the skilled artisan with significant guidance with respect to each of the components necessary to practice the invention. Thus, in accordance with the legal standard set forth in *Wands*, and for the sake of argument even if the art were to be held to be unpredictable, the skilled artisan in possession of Applicants' application would be enabled to practice the invention without undue experimentation.

In summary, Applicants respectfully submit that the specification is sufficient to enable one of ordinary skill in the art to practice the claimed invention without undue experimentation, and that the claims fully comply with all the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection Under 35 U.S.C. §112, First Paragraph – Written Description

According to section 5 of the outstanding Office Action, claims 1-4, 6, 8-9, 32-35, 38-43, 45 and 47-49 presently stand rejected under 35 U.S.C. §112, first paragraph for lack of written description. Applicants submit that claims 6, 38 and 45 have been cancelled thereby rendering this rejection moot with respect to these claims. Applicants respectfully traverse this rejection to the extent that it is maintained over the remaining claims, as amended.

The Office Action states that "[g]iven the lack of a written description of any additional representative species of tetrapyrrole derivative and anti-vascular endothelial growth factor antibody for the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus." Although Applicants disagree, Applicants have amended independent claims 1, 33 and 41 and the claims depending therefrom to recite that (i) the photosensitizer useful in the practice of the claimed invention is selected from the group consisting of a lutetium texaphyrin photosensitizer and a benzoporphyrin derivative photosensitizer, and (ii) the anti-angiogenesis factor is selected from the group consisting of angiostatin and an antibody that binds preferentially to vascular endothelial growth factor.

The Office Action infers that lutetium texaphyrin is the only tetrapyrrole derivative sensitizer described in the application. Applicants direct the Office to the paragraph bridging pages 9 and 10 of the application , which provides a list of exemplary tetrapyrrole derivative photosensitizers. Claims 1, 33, and 41, however, have been amended to recite the use of a lutetium texaphyrin photosensitizer and a benzoporphyrin derivative photosensitizer, both of which are classified in the application as a tetrapyrrole derivative.

In view of the amendments to the claims, the previous discussion with regard to enablement, together with the scope and content of the articles discussed therein, Applicants submit that the Applicants clearly were in possession of the invention at the time the application was filed. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejections Under 35 U.S.C. §103(a)

According to section 8 of the outstanding Office Action, claims 1-4, 6, 8-9, 32-35, 38-43, 45, and 47-49 presently stand rejected under 35 U.S.C. §103(a) over U.S. Patent No. 6,162,242 (the "'242 Patent") in view of U.S. Patent No. 5,733,876 (the "'876 Patent"). Applicants submit that claims 6, 38 and 45 have been cancelled thereby rendering this rejection moot with respect to these claims. Applicants respectfully traverse this rejection to the extent that it is maintained over the remaining claims, as amended, and respectfully request that this rejection be reconsidered and withdrawn.

Applicants' claimed invention is directed to a method of treating unwanted choroidal neovasculature comprising endothelial cells. The method comprises (i) administering to a mammal in need of such treatment an anti-angiogenesis factor of angiostatin or an antibody that binds preferentially to anti-vascular endothelial growth factor, (ii) administering to the mammal a tetrapyrrole derivative photosensitizer of lutetium texaphyrin or benzoporphyrin derivative, and (iii) irradiating the CNV so as to activate the photosensitizer which then causes occlusion of the CNV.

35 U.S.C. §103 states that the subject matter, taken as a whole, must be considered when evaluating the patentability of an invention under 35 U.S.C. §103. The case law on this is quite clear. In addition, the consistent criteria for the determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that the claimed subject matter should be carried out, and would have a reasonable likelihood of success. Both the suggestion and the expectation of success must be founded in the prior art, not in Applicant's disclosure. *In re Dow Chemical Company*, 5 USPQ2d 1529, 1530 (Fed. Cir. 1988).

Furthermore, the case law is clear where references are combined. In order for a combination of references to render an invention obvious, it must be obvious that their teachings can be combined. That is, obviousness cannot be established by combining the teachings of the prior art to produce claimed invention, absent some teaching, suggestion or incentive in the art supporting the combination. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). Citing references which merely indicate the isolated elements recited in the claims is not a sufficient basis for concluding that the combination would have been obvious. *Ex parte Hiyamaizu*, 10 USPQ2d 1393 (BPAI 1988). Applicants submit, for the reasons set forth below, that nothing in any of the references suggest their combination, and nothing in any of the references lays the foundation for a reasonable expectation of success, were such a combination to be made.

The '242 Patent discloses a method of performing PDT. The method involves (i) administering a photosensitizer, (ii) allowing sufficient time for the photosensitizer to be released from abnormal blood vessels into a site adjacent the abnormal vessel while maintaining the photosensitizer within normal blood vessels, (iii) transiently constricting the normal vessels to displace the photosensitizer out of the normal vessels, (iv) phototreating the site to treat the abnormal vessel having photosensitizer in the adjacent tissue, and (v) restoring the normal vessels to an unconstricted state. According to the '242 Patent, the method may also include the use of, for example, a vessel occluding agent, for example, adenosine diphosphate. The '242 Patent, however, does not teach or suggest combining the PDT method with an anti-angiogenesis factor.

The '876 Patent discloses using angiostatin to inhibit angiogenesis and to inhibit endothelial cell proliferation. The '876 Patent, however, fails to teach or suggest including angiostatin in a PDT method for treating unwanted CNV.

At the outset, Applicants submit that there is no teaching or suggestion whatsoever in any of the applied references that would motivate the skilled artisan to "substitute the coagulation factor" in the '242 Patent with angiostatin as taught in the '876 Patent. Furthermore, Applicants submit that, even if such a combination were to be made, the skilled artisan would have no reasonable expectation that such a method would be effective at occluding CNV.

Applicants submit that agents that promote the formation of thrombi or clots as discussed in the '242 Patent (for example, adenosine diphosphate) are completely different (both in structure and function) than angiostatin as discussed in the '876 Patent. The occluding agent of the '242 Patent occludes blood vessels, for example, by promoting blood clot formation. In contrast, angiostatin as discussed in the '876 Patent blocks the growth of new blood vessels. Applicants submit that these are two completely different physiological effects. Applicants submit that there is no reason for the skilled artisan to believe that *an anti-angiogenesis agent, which acts to inhibit the growth of new blood vessels, would be useful at occluding already existing blood vessels, as required by the teachings of the '242 Patent*.

The Office Action indicates that the "combined teachings of the '242 patent and the '876 patent provide clear direction, motivation and expectation of success in treating unwanted choroidal neovasculature using the specific tetrapyrrole derivative and the specific anti-angiogenesis factor." Applicants respectfully disagree and submit that the skilled artisan, based on the differences in their respective modes of action, would not have been motivated to replace adenosine diphosphate, *which potentiates blood clot formation in already existing vessels* with an angiogenesis factor, *which prevents the growth of new blood vessels*.

Furthermore, there is no teaching or suggestion in the applied references that would provide the skilled artisan with a reasonable expectation that a PDT-based method, when combined with an anti-angiogenesis factor, would be effective in treating CNV. Applicants submit that the motivation to practice the claimed invention coupled with the reasonable

expectation of success articulated in the Office Action represents impermissible hindsight reconstruction of the claimed invention, which would not have been possible without the benefit of the Applicants' disclosure. The courts have held that one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *In re Fine*, 5 USPQ2d at 1600.

Moreover, there is nothing that would suggest that the combined method would be more effective than the sum of each of the separate treatments of PDT and the administration of anti-angiogenesis factor. These unexpected findings are shown in both the application as filed and in citation C115, already made of record. Applicants respectfully disagree with the statements in the Office Action that Applicants have provided "insufficient evidence that the methods of the instant claims would differ in an unexpected manner from those described in the references."

Citation C115, for example, discloses *in vivo* experiments which demonstrate that angiostatin can potentiate the efficacy of Verteporfin PDT to close CNV. At the doses used in these experiments, angiostatin alone did not prevent the growth of CNV. In contrast, continuous pretreatment with angiostatin potentiated significantly the efficacy of Verteporfin PDT for CNV closure relative to a PDT alone. For example, when PDT alone was conducted using a fluence of $10J/cm^2$, about 40% of the lesions lacked angiographic leakage. In contrast, when the PDT was conducted following continuous administration of angiostatin, at least about 90% of the lesions lacked angiographic leakage. Applicants submit that these syngeristic results could not have been predicted based on the teachings of the applied references. Accordingly, Applicants submit that, even if the skilled artisan were motivated to combine the teachings of the '242 Patent with those of the '876 Patent, the skilled artisan would have no reasonable expectation that the claimed method would be so effective at closing unwanted CNV. Applicants submit that none of the applied references, either alone or in combination, teach or suggest this type of synergism.

In view of the foregoing, Applicants respectfully submit that the claimed invention would not have been obvious to those skilled in the art at the time the invention was made, and respectfully request that the rejection based on the '242 Patent and the '876 Patent be reconsidered and withdrawn.

According to section 9 of the outstanding Office Action, claims 1-6, 8-9, and 32-49 presently stand rejected under 35 U.S.C. §103(a) over either U.S. Patent No. 5,707,986 (the "'986 Patent") or U.S. Patent No. 6,270,749 (the "'749 Patent") in view of the '876 Patent. Applicants submit that claims 6, 38 and 45 have been cancelled thereby rendering this rejection moot with respect to those claims. Applicants respectfully traverse this rejection to the extent that it is maintained over the remaining claims, as amended, and respectfully request that this rejection be reconsidered and withdrawn.

Applicants respectfully submit that, for the reasons set forth below, there is no teaching or suggestion in any of the applied references that suggest their combination, and that nothing in any of the references lays the foundation for a reasonable expectation of success, were such a combination to be made. Applicants further submit that the claimed invention has unexpected properties that would not have been foreseeable by the skilled artisan at the time the invention was made.

The '986 Patent discloses a PDT method employing a green porphyrin dye for the treatment of unwanted CNV. The '749 Patent discloses a PDT method employing a texaphyrin dye for the treatment of CNV. Neither the '986 Patent nor the '749 Patent teach, suggest or in any way infer combining their respective PDT methods with an anti-angiogenesis factor.

The '876 Patent, as discussed above, discloses using angiostatin to inhibit angiogenesis and to inhibit endothelial cell proliferation. The '876 Patent fails to teach, suggest or even infer including angiostatin in a PDT-based method for treating unwanted CNV.

For reasons analogous to those discussed previously, Applicants submit that there is nothing in any of the applied references that would motivate the skilled artisan to combine the teachings of the '986 Patent or the '749 Patent with those of the '876 Patent. For sake of argument only, even if the teachings were combined as suggested in the Office Action, Applicants submit that the skilled artisan would not reasonably expect that the method would be so effective at closing unwanted CNV. As discussed before, Applicants submit that the motivation to practice the claimed invention coupled with the reasonable expectation of success

articulated in the Office Action represents impermissible hindsight reconstruction of the claimed invention, which would not have been possible without the benefit of the Applicants' disclosure.

Furthermore, Applicants respectfully disagree with the Office Action, which states that Applicants have provided "insufficient evidence that the method in the instant claims would differ in an unexpected manner from those described in the references." Applicants submit that none of the applied references, either alone or in combination, teach or suggest the type of synergism discussed in C115. Applicants submit that the skilled artisan after reviewing the applied references would have no reason to believe that the claimed method would be so effective at closing unwanted CNV.

In view of the foregoing, Applicants respectfully submit that the claimed invention would not have been obvious to the skilled artisan relying on the teachings of the '986 Patent, the '749 Patent and the '876 Patent, either alone or in combination, and respectfully request that this rejection be reconsidered and withdrawn.

Objection of Claims 1, 32 and 41

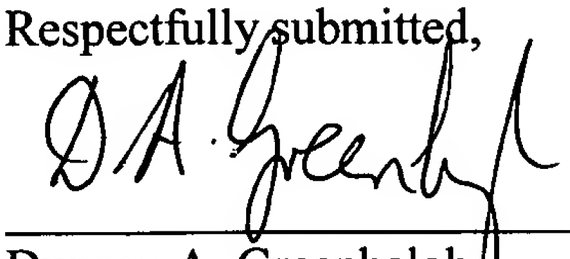
According to section 11 of the outstanding Office Action, claims 1, 32 and 41 are objected to for reciting a non-elected embodiment, the anti-vascular endothelial growth factor antibody. Applicants respectfully request that this objection be held in abeyance.

In the April 25, 2002 Preliminary Amendment, Applicants elected the Group I claims for further prosecution. In addition, Applicants made a ***species*** election for the disorder (age-related macular degeneration), the anti-angiogenesis factor (angiostatin), and the photosensitizer (lutetium texaphyrin). In the Preliminary Amendment, Applicants requested that upon allowance of generic claims corresponding to the elected species, Applicants may claim addition species as provided by 37 C.F.R. §1.141 and as set forth in M.P.E.P. §806.04(h). Accordingly, Applicants request that claims directed to the non-elected species be allowed if they correspond to one or more allowed generic claims.

CONCLUSION

In view of the foregoing, Applicants respectfully submit that the case is in condition for allowance. Early favorable action is respectfully solicited.

Respectfully submitted,



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